ARCHIVES OF PEDIATRICS

August 1961

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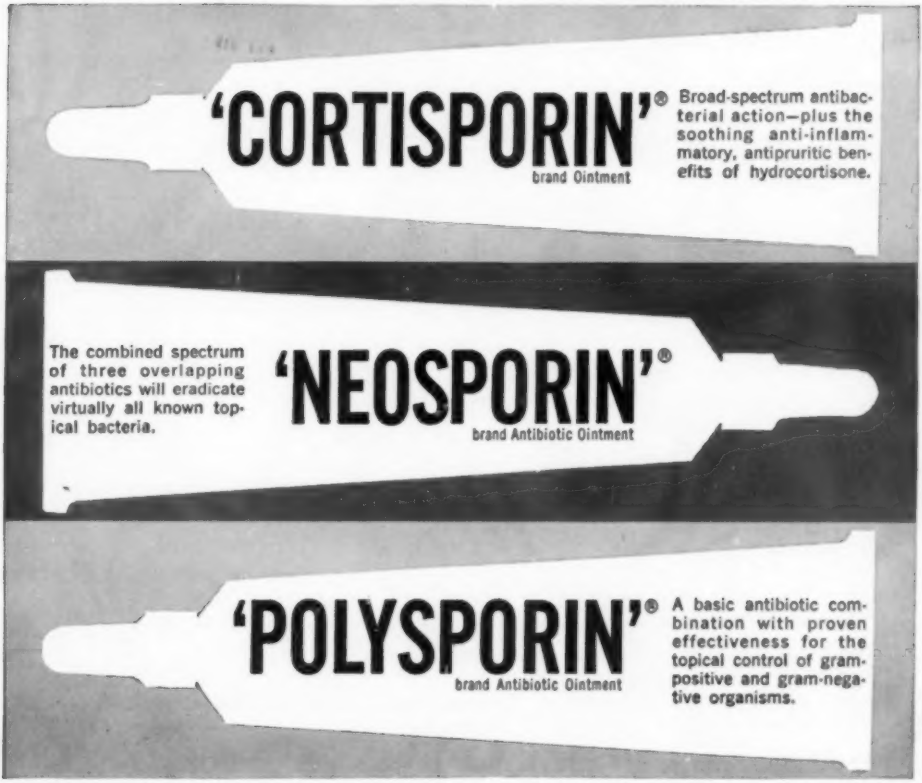

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CONTENTS

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The Cover . . .

World Health Organization Headquarters, Geneva, Switzerland . . . See Page 6
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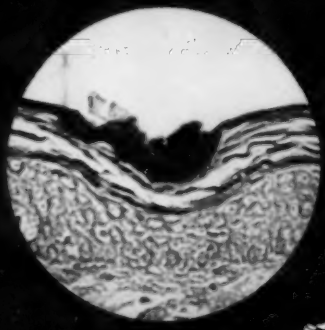

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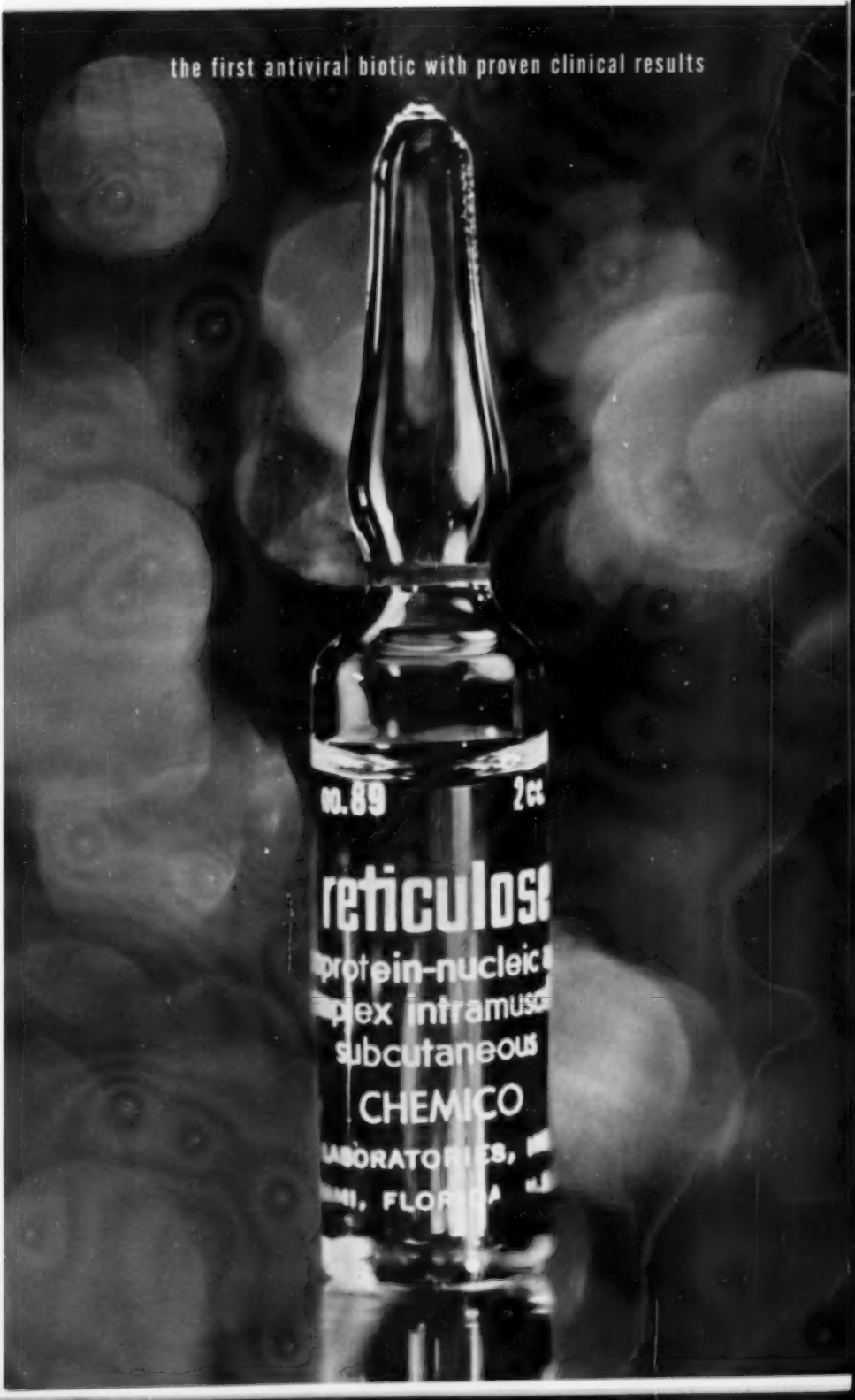
1. Spoor, H. J.: New York St. J. M. 60:2863, 1960.
2. Wiese, H. F., et al.: J. Nutrition 66:345, 1958.
3. Smith, L. W., et al.: Amer. J. Med. Sc. 237:600, 1959
4. Nutrition Reviews 17:136, 1959.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Bibliography: 1. Anderson, R. H., Thompson, R. M., Treatment of Viral Syndromes, Va. Med. Mo. Vol. 84-347 353, 7-57. 2. Scientific Exhibit, Va. State Medical Soc., Washington, D.C. Oct. 1957. 3. Symposium Viral Diseases, Miami, Fla. September, 1960. 4. Reynolds, R. M., Vaccinia, Archives of Pediatrics, Vol. 77 No. 10 Oct. 1960. 5. Wegryn, S. R., Marks, Jr. R. A., Baugh, J. R., Herpes Gestationis, American Journal Ob. and Gyn., Vol. 79 Apr. 1960.

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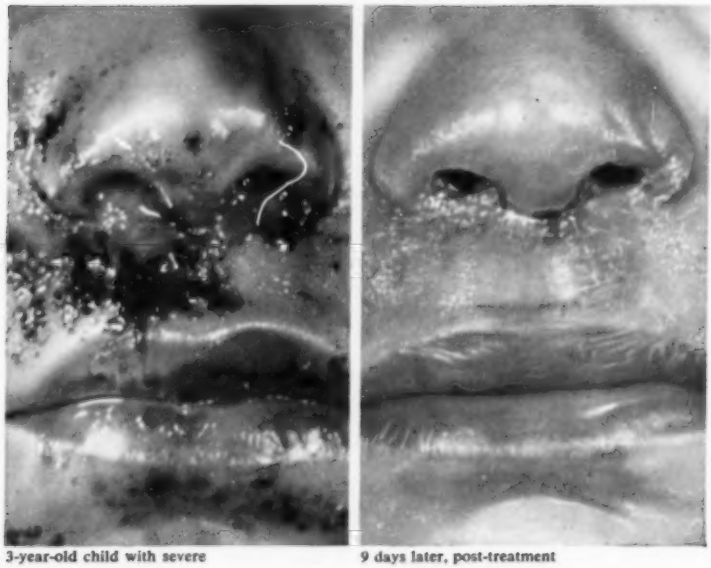

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The Cover . . .

Housed in a section of the Palais des Nations, Geneva, Switzerland (also the site of the European office of the United Nations) are the headquarters of **The World Health Organization** (WHO), the inter-governmental agency whose aim, keynoted in its Constitution, is "The health of all peoples is fundamental to the attainment of peace and security".

WHO works with the **U.N. Food and Agriculture Organization** (FAO) on nutrition problems and ways of improving peoples' everyday diets by adding locally-available protein foods so essential for health and growth. FAO's idealistic Charter goal is to accelerate the tempo in underdeveloped countries toward securing increased production of food and better standards of nutrition. FAO headquarters are in Rome, Italy.

Readers will undoubtedly be especially interested in this issue's timely presentation of a study by Dr. Heinrich Lehndorff on present problems related to Kwashiorkor—the intensely important subject to which WHO and FAO have lent dedicated attention during the past few years.

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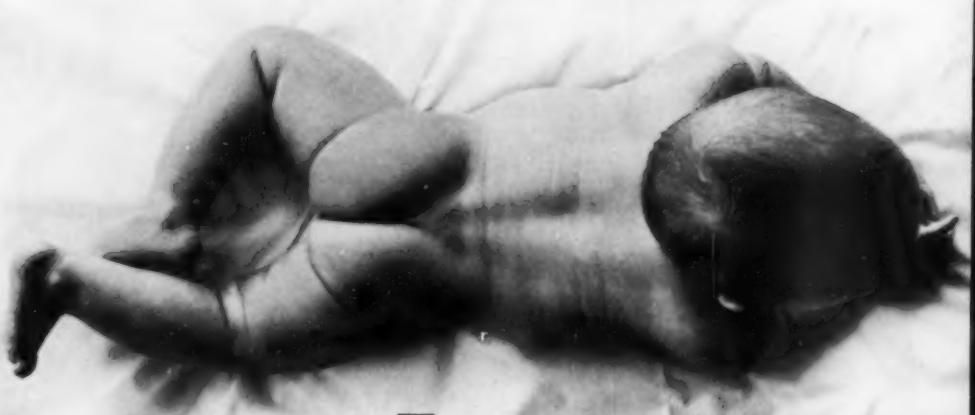
ARCHIVES OF PEDIATRICS — 200 Park Avenue So., New York 3

are opiates now outmoded in pediatric diarrhea?



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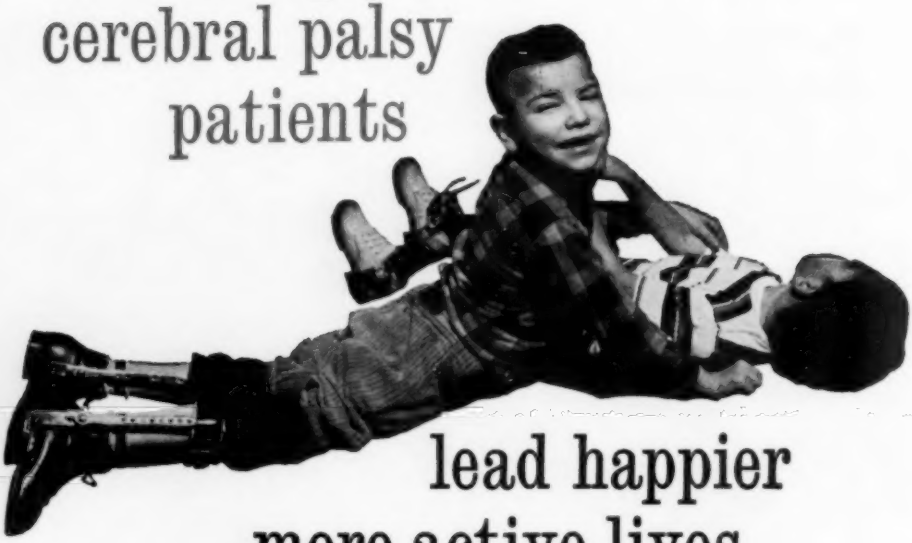

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1. Phelps, P.M., Arch. of Ped., 76:243-250, June, 1959.
2. Spears, C. A., Annals of N.Y. Acad. of Sc., Mar. 30, 1960, Vol. 86.

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*T.M.

Kwashiorkor . . .

PRESENT PROBLEMS

This review of Kwashiorkor has been received for publication at a most opportune time, in view of the intensified worldwide interest in this primarily African disease. A student of this subject, the author speaks with authority.

H. Lehndorff, M.D.*

New York

KWASHIORKOR is a clinically well defined morbid entity with a demonstrable pathology starting soon after weaning. It is almost endemic in African infants, and 85% of all children are affected. Certain tribes are convinced that kwashiorkor is an unavoidable children's disease like measles—a phase in life every infant has to go through. Inadequate statistics make it impossible to give correct figures concerning the mortality rate. Death in infants, if reported at all, is ascribed to infectious diarrhea, dysentery, malaria, tuberculosis, ascaridiasis or marasmus. The high rate of infantile morbidity and mortality in the tropics is not caused by infectious diseases, but by malnutrition.

This article will be restricted to a discussion of some controversial problems and the position of kwashiorkor among other malnutrition affections in adults and in the white race. There are more than 800 excellent papers available, such as those of Trowell, Davis and Dean (1954)[1], Fuhrmann (1958)[2], Tamaels (1959)[3] and recently, Frontali (1960)[4]. In addition, studies initiated by the WHO and FAO** as a monograph series, the panel discussion on malnutrition (1958) and on malabsorption (1957) and finally, the report of the WHO and FAO Expert Commission on Nutrition.

NOMENCLATURE

The term kwashiorkor was coined by Cecily Williams in 1935[5]; it was the name used by the natives in Ghana. The WHO has endorsed it and the mystic-sounding name became generally accepted and will probably remain in use until better knowledge may produce a better name. Some authors translate it "golden or red child".

* Former Lecturer on Pediatrics, University of Vienna, Austria. Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

** WHO, World Health Organization. FAO, Food and Agricultural Organization.

A polyglot vocabulary exists. More than 50 names illustrate the fact that many observers described the same disease using different names according to their personal evaluation of a single manifestation. The following is an incomplete list:

> Malnutrition, malignant or third degree malnutrition, nutritional edema, infantile weaning edema, wet marasmus, dyschromic edematous syndrome, infantile pellagra, pellagroid beriberi, fatty liver disease, multiple deficiency or pluricarential syndrome, les enfants rouges, starch food disease. European names are: Mehlnährschaden, Eisweissmangeldystrophie, "distrofia da farina". Names used by local tribes, e.g., chichico, shibi gadalki and others are only of historical or linguistic interest.

Misunderstanding is partly to blame for this chaotic nomenclature. Early observations were published in local African medical journals and were not read by physicians in other parts of Africa and certainly nowhere else in the world. At this point, a few remarks about terms commonly used in nutritional disorders seem in order.

Marasmus is a most unfortunate term that indicates a high degree of waste of body tissue resulting in general weakness. Some authors use kwashiorkor and marasmus interchangeably. Some experts consider it as a phase in the course of kwashiorkor, appearing after the disappearance of the edemas; others use the name synonymously with kwashiorkor. Béhar tried to visualize the relation between marasmus and kwashiorkor in his "pyramide", published Ann. Acad. Sci. 69: 1957.[6] The apex indicates the zone of healthy infants, the broad basis shows on one side marasmus, on the other kwashiorkor and between, the zone of "marasmic kwashiorkor". On the left side of the pyramid-basis appears marasmus, with the predominant signs: growth-retardation, weight-drop, musculature-atrophy. On the other end in addition, are psychic changes, hair alterations, dermatoses, hypoproteinemia, fatty liver, gastrointestinal disturbances, the symptomatology of "classic kwashiorkor." Between them is the zone of "marasmic kwashiorkor". It seems that the majority of reported tropical kwashiorkor as well as the European cases in the white race belong to the intermediary group. Some experts on malnutrition in Africa, and European clinicians, especially Frontali[4] and his school, proclaim complete identity of kwashiorkor in Africa and Mehlnährschaden in Europe; these are not *toto coelo* different entities, but variants of the same affection; differences in appearance can be

attributed to racial, climatic, economic conditions, local feeding habits and environment. The biochemical alteration, the hypoproteinosis unites all types.

Mehlnährschaden (Czerny 1906)[7] literally translated indicates "damage by nutrition with flour", but it is not the surplus of flour that causes the malnutrition, but the deficit of protein. The condition was well known by pediatricians in Europe during the starvation periods during and after World War I. It resulted in various types of atrophy and marasmus. This condition was practically unknown in England or America, since there were different feeding habits and infant's diet included always some amount of protein.

Dystrophy is a milder degree of atrophy. In Germany the term indicates a state of body waste; in the English medical literature, dystrophy is associated with a degenerative condition as in muscular dystrophy.

Atrophy presents identical linguistic difficulties. In German pediatric literature it designates the terminal phase of chronic malnutrition. The same term is used for an anatomic condition describing waste of body substance.

Malnutrition also has a two-fold meaning. It means faulty composition of the food offered to the infant, and at the same time, it means the results of this feeding habit. Some authors use the term malnutrition, adding malignant or third-degree to describe a variation closely related to kwashiorkor. (Béhar)[6]. Gomez[8] offers the following definition for malnutrition: "The term denotes the state of an organism in which the tissue cells are chronically on the border of deficiency".

Eiweissmangeldystrophie was proposed by Fanconi[9]. It signifies protein-deficiency dystrophy—a name too long and ungainly.

Hypoproteinosis was used in 1951 by Lynch and Snively for a different type of malnutrition in children who obstinately refused solid food and insisted on bottle feeding.

PATHOGENESIS

Kwashiorkor is a well defined morbid entity, affecting infants after weaning, caused by malnutrition, by feeding the child with a protein-deficient nutriment; it is a protein deficiency disease characterized by a relative lack of calories and commonly by other deficiencies. This tropical disease exhibits such a great number of

peculiarities in clinical appearance that it makes it difficult to attribute all of them to a single etiologic agent. It has been suggested that besides the deficiency of biologically valuable protein and absence of one or a group of essential amino acids, there must be unknown factors active.

(1) *Breast Starvation:* The primary damage is originated by prolonged breast feeding without additional food. A typical anamnesis is reported in every case. Newborn babies are nursed by their mothers for one or two years or longer. Exclusive breast-milk feeding without additional food after the half year, the period of increased need by the rapidly growing organism, is not only insufficient in calories, but also deficient in protein. The mother is often exhausted by overwork, undernourishment, disease, frequent childbearing; her milk is deficient in quantity and quality, that is, lacking in proteins, vitamins, and essential amino acids. Prolonged breast feeding without additional protein leads to breast starvation. This condition forms the basis on which the kwashiorkor disease develops and was named Pre-Kwashiorkor. This is a common condition in weaned babies in Africa and it is difficult to draw a sharp line between health and pre-kwashiorkor. The name "pre-kwashiorkor" will probably disappear from the nomenclature; in the recently-published textbook on "Non-infective disease in Africa" Trowell[1] describes the condition as Infantile Malnutrition; the list of synonyms includes malnutrition grade I and probably II (Gomez)[8]; mild, incipient or pre-kwashiorkor. The condition appears in children who after a successful period of feeding on the breast cease to grow because of poor diet. The majority of African infants pass through a period of infantile malnutrition.

(2) *Infantile Malnutrition:* The most important pathogenetic factor is feeding the weaned child with an inadequate diet: rich in carbohydrates, deficient in valuable protein, amino acids and vitamins. The diet of the weaned child consists everywhere in the tropics of pap, porridge, gruel or soup prepared from cereals chosen from local cultivation: maize, rice, millet, sorghum, or tapioca, jam, cassava; sugar is often added, but never milk. In some districts, the children are offered bananas, potatoes, but never green vegetables. The diet of the weaned infant consists of carbohydrates with a minimum of fat and practically complete absence of good, i.e., animal protein. The malnutrition-effect in starch-diet is not the result of a surplus of carbohydrates, but of a deficiency in biologically valuable protein; that means a protein, which must be in-

gested, digested, absorbed and finally utilized for restitution and for building up body cells. Malnutrition is literally a descriptive term; it indicates that a deficient diet was given to an infant during the period of increased need. It might be advisable to distinguish between primary and secondary deficiency in the diet.

1a) *Primary deficiency* resulting from insufficient food intakes; severe anorexia, poor feeding habits caused by economic conditions, superstition.

1b) *Secondary deficiency* caused by insufficient internal digestion and absorption. In kwashiorkor both factors are active. Loss of food substance by the rapid passage through the intestines by diarrhea; absence of vital substance, amino acids, vitamins and enzymes, indispensable for food absorption. This places kwashiorkor in the group of malabsorption diseases, an acknowledged entity among the deficiency diseases. However, malnutrition remains the primary factor; kwashiorkor begins with malnutrition and ends as malabsorption.

There is a common superstition that in case of a new pregnancy, continuation of nursing would harm the fetus, so the sibling must be removed. The infant who has lived in intimate contact with his mother day and night becomes suddenly abandoned. Cow's milk would be the natural and best source of protein, but it is only available in cattle-breeding districts; it is an expensive nutrient and Africans are not accustomed to spending money for food. There is among the uneducated people a high degree of mistrust of milk, attributed to the supposed indigestibility of cow's milk casein. And finally the tropical heat combined with the unsanitary environment might transform milk into a dangerous food. The difficulties of general milk distribution seem to be insurmountable. Continuation of cereal diet without protein leads gradually from infantile malnutrition to the kwashiorkor-disease. It is difficult to decide which of the clinical manifestations could be called early signs. The infants are admitted to a hospital or medical center usually in an advanced phase of the disease after a long period of malaise, when diarrheas, edemas and skin eruptions point to the seriousness of the condition. Weakness and indifference prohibit the mother from carrying the sick child to a distant hospital, and they are often ashamed to present an ugly child to a white doctor.

(3) *Stress:* During this stage, stress may provoke the appearance of kwashiorkor manifestations. The sudden and inexplicable

loss of maternal love and care will produce the characteristic psychic alterations; apathy and sadness and most important, loss of appetite, the refusal of food. Stress is a contributory factor during the occurrence of acute febrile diseases, as measles, whooping cough, a malaria attack, etc.

(4) *Intestinal Infections:* The other factors are intestinal infections, practically unavoidable, due to the tropical heat and the bad hygienic surroundings; the resulting diarrheas produce a variety of effects in metabolism; (a) the rapid passage through the intestinal canal prohibits sufficient absorption and digestion, contributing to starvation, and (b) finally resulting in waste of body substance, especially of fat, muscular atrophy, general weakness, called marasmus; (c) electrolyte imbalance: loss of water, minerals—potassium, calcium, iron—explain the clinical manifestations, dehydration, anemia, etc.

(5) *Hypoproteinemia:* The biochemical alteration, that is, the lowered level of protein support in the food (malnutrition), and loss of protein from diarrhea; it results in impaired absorption (malabsorption). The end result is edema, the primary cause of which is the changed osmotic pressure.

(6) *Histopathologic Alterations:* There may be a combined effect—damage caused by the protein deficiency and inflammatory reactions in the intestinal mucosa by diarrhea (bacteria or toxins).

(a) Pancreas: Degeneration and atrophy of the excreting cells is followed by a stoppage of enzyme production with resultant interference in digestion, absorption and utilization of food. There is no complete agreement, but there is a probability that the pancreas might be the first organ damaged, which in turn affects liver and other systems.

(b) Liver: The fatty liver is an early manifestation appearing in every case of malnutrition resulting from protein deficiency.

(c) Intestines: In addition to the atrophic thinness, cystic degeneration of the cell layer in the submucosa has been observed; this damage may be a part of the general atrophy or the result of the irritating diarrheas.

(7) *Amino Acids:* The absence of essential amino acids, vitamins and enzymes inhibits absorption by the intestinal mucosa cells.

(8) *Malabsorption and Mal-utilization:* will in turn produce or aggravate the manifestations of kwashiorkor; insufficient supply of building blocks for restitution and growth will cause failure of gain in weight and height and produce marasmus.

(9) *Discoloration of Hair:* The absence of special amino acids necessary for melanin explains the discoloration of the black negro hair. Some peculiarities of the dermatoses are probably the result of a vitaminoses accompanying the protein deficiency in kwashiorkor.

Feeding mice and rats with various types of protein defective diets has produced marasmus, but not kwashiorkor. Most important results can be expected from experimental studies with amino acids: aminograms of all the different types of foods, their need and action in disease, convalescence, the content in apparently healthy siblings of a kwashiorkor patient, in their parents, etc. More studies might clarify the fact, that in protein malnutrition-disease, it is not the absence of one or a group of amino acids that is to blame, but their imbalance. The question of great importance in pathogenesis is the aberration of amino acid metabolism. Is an inborn error active in kwashiorkor as has been found in phenylketonuria, maple syrup disease and other metabolic disorders? Or is such an aberrant anlage acquired by an intercurrent factor—unknown and unexplored?

There has been insufficient bacteriologic study of the diarrhea in kwashiorkor; there might be a specific toxin in the African disease, present in the stools or originating in the afflicted mucosal endothelium.

Future experience will tell whether the transfer of kwashiorkor from the list of malnutrition diseases to the group of malabsorption conditions might help toward a better understanding.

BIOCHEMISTRY

The profound alteration of the biochemistry has become the central feature of the kwashiorkor disease in Africa, as well as in the malnutrition diseases in Europe. Hypoproteinemia produced by insufficient supply of protein in the food was recognized as the cause of the malnutrition, edema and other manifestations. A survey of the literature shows the increasing interest; the majority of the publications during the past years are concerned with the serum proteins and their relation to kwashiorkor and the importance of different proteins and amino acids in successful therapy.

(a) Total serum protein shows a reduction to 3.0 G% or less. (Normal 7.5 G%).

(b) This is caused chiefly by serum albumin reduction to 1.5—2.0 G% (Normal 4.2 G%).

(c) Serum globulin is diminished to a lesser degree: 2.5 G% (Normal 3.3 G%). These changes produce the characteristic alteration of the albumin: globulin ratio.

(d) Gamma Globulin shows a slight tendency to increased values.

(e) All serum lipids are reduced: total, phospholipids, neutral fat, total and free cholesterol.

It is of importance to state that these severe alterations are reversible; following a correct dietary treatment, they become normal with astonishing promptness; total proteins increase 56%, serum albumin 90% within a week. (Frontali)[4].

(f) Water and electrolyte imbalance: contributing factors are vomiting, diarrhea and the sudden disappearance of edema; loss of minerals, especially sodium, potassium, iron and calcium are important factors in the pathogenesis.

(g) Vitamin levels in the blood: low figures for thiamine and riboflavin are reported.

(h) N-balance: recent studies point to impaired absorption.

Amino Acids: The role of amino acids in the pathogenesis and treatment of kwashiorkor is very important. The recently published monograph by Holt[10] and co-workers, offers a complete review of present knowledge; the need of the growing organism for protein and amino acids and the deficiency of these substances in the starchy food given to the children after weaning is emphasized. The pathogenesis of kwashiorkor can be understood as protein deficiency in the food; it is not a simple deficiency in quantity but of specific factors, the absence of one or a group of amino acids, indispensable for the metabolism. A certain number of amino acids must be available for the digestion of the ingested food, to prepare it for absorption and utilization. Present knowledge about the amount of available amino acids in the food offered to infants after weaning is incomplete. Aminograms reported by Frontali[4] reveal rice proteins: deficient in lysine and histidine; maize; insufficient

amount of lysine and tryptophan. Potato and jam: insufficient portion of methionine and cystine. Peas and beans: deficient in lysine, methionine, cystine, troyptophan. The only exception are soybeans, which show the highest percentage of the substances mentioned. The role of specific amino acid deficiencies in producing clinical manifestations is based chiefly on animal experiments. Deficient essential amino acids in human food for infants is constantly followed by anorexia and failure to gain in weight and growth. Imbalance of the amino acid composition is perhaps of greater importance; amino acids play an important role in the activation of enzymes in the intestinal tract and their absence may contribute to the development of diarrheas. Absence of certain amino acids may be a factor causing discoloration of the hair.

HISTO-PATHOLOGY

Liver: The outstanding feature is the fatty metamorphosis, the steatosis (Fig. 1) demonstrable in every case post-mortem as well as by biopsy. The lobular structure is destroyed, the cells transformed to big vacuoles containing fat droplets; proliferation of the interlobar connective tissue forms the picture of "stellate fibrosis."

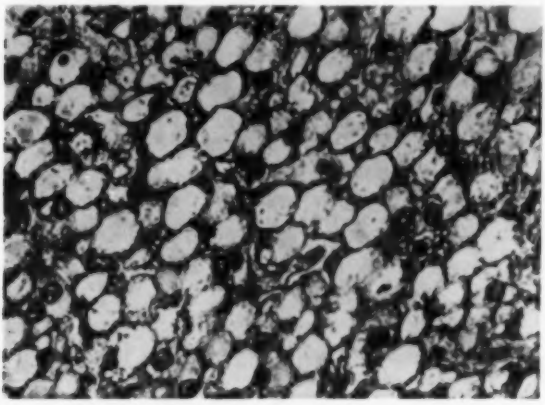

FIG. 1: Typical picture of steatosis of the liver.
(From Frontali's monograph)

This severe liver damage is completely reversible. Adequate protein diet restores normal histology within a short time. Liver steatosis is not restricted to the African kwashiorkor; it has been observed usually in a far lesser degree in other types of hypoproteinosis.

Pancreas: A high degree of atrophy is the most striking manifestation (Fig. 2). In severe cases the organ is reduced to a small band of a fibrocollagenous scar tissue; the exocrine lobuli are atrophied, whereas the Langerhans islets appear intact. The atrophy is followed by a fibrinoid proliferation of the interstitial tissue. The consequence is a stoppage of production and secretion of the enzymes necessary for the digestion and utilization of food.

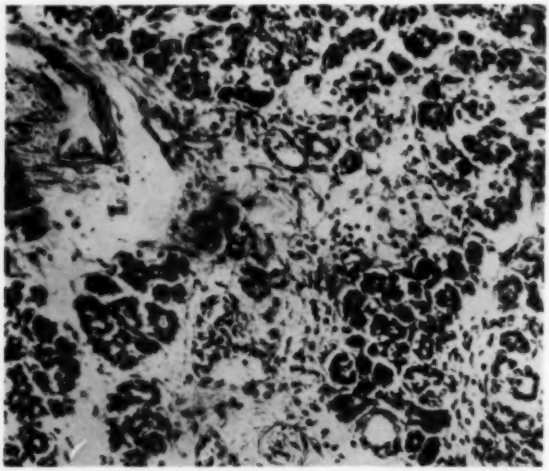

FIG. 2: Pancreas—high degree of atrophy, damage to the exocrine system, extensive fibrocollagenous scarlike tissue. (From Ergebnisse der Inneren Medizin und Kinderheilkunde, Neue Folge Bd. 12, 1960).

Gastro-Intestinal Tract: In contrast to the great number of examinations of liver and pancreas histologic studies of the intestinal mucosa have been started only recently. Earlier papers reported only a thin, translucent wall with occasional inflammatory patches. Diamond and Vallbona[11,12] describe "in the colonic submucosa scattered cystically dilated glands lined by flattened endothelial-like cells". In the upper digestive tract, tongue, mouth mucosa, esophagus, there are striking irregularities in the epithelium, a combination of patchy atrophy associated with local epithelial hyperplasia and papillomatosis.

These alterations in the gastrointestinal mucosa could be the result of permanent irritation by diarrhea, but it could also be the primary lesion, originated by malnutrition.

Similar lesions of the endothelium have been observed by some authors in avitaminoses and in endocrine disorders, as in hypothyroidism. These authors conclude that such lesions could be an integral part in the histopathology of kwashiorkor. These histopathologic findings suggest a reasonable hypothetic assumption. Insufficient protein supply to the need of the rapidly growing organism damages every cell in the body, but first and most intensively the pancreas. The atrophic destruction of the exocrine glands arrests the secretion of all the enzymes indispensable for digestion of the ingested food. In turn the activity of the liver function becomes impaired. Absence of the ferments in the stomach, duodenum, and intestines could explain the phenomenon of malabsorption, faulty utilization of the nutritional elements, which finally must produce the phenomenon of marasmus.

Deaths occurring shortly after admission to the hospital can be attributed to exhaustion of the marantic, dehydrated infant, or to shock or electrolyte imbalance, or to potassium deficiency initiating cardiac insufficiency. If the infants have survived the first hospital days, there is the danger of terminal pneumonia. Too freely administered protein can be responsible for sudden death. Patients with severe kwashiorkor are extremely labile and may die from even a minor shock. (Dean)[1]. There are cases of unexplained sudden death during convalescence; they could be attributed to hypoglycemia. In later periods, infections, tuberculosis and malaria are fatal events.

Follow-up studies: Only recently some workers have tried to clear up the question of sequelae in kwashiorkor. (Moodie, Wellbourne)[13]. It seems that infants recovering from kwashiorkor remain healthy. There is no proof that liver damage may continue and produce the cirrhotic liver in adult Africans.

SYMPTOMATOLOGY

(1) Arrest of growth: This is by common consent, the earliest sign of the disease. The babies are born slightly subnormal in length and weight, but it is the insufficient protein supply which causes complete cessation of growth. The figures for weight are often misleading; the infants look fairly well nourished, this appearance being caused by manifest or hidden edema. The cessation of growth is an important clinical manifestation.

(2) Change of the infant's mental attitude and behavior: This

is another early manifestation, important for diagnosis and pathogenesis. It is pathognomonic of African kwashiorkor and similar malnutrition diseases in the tropics; apathy and sadness, usually in a far milder degree, has been observed in European hypoproteinoses (Frontali)[4]. The profoundly changed psychic attitude can be understood by the fact that the infant is not only removed from his mother's breast, but completely abandoned. The mother no longer fondles him or plays with him, and sometimes does not even talk to the abandoned child. This involves an intensive shock. Expert African physicians believe that stress and loss of the maternal love and care are important etiologic factors. A healthy negro infant fights loudly and energetically against examination; the kwashiorkor patient does not react at all; he is apathetic, peevish, does not talk or smile, shows no interest in other children in the ward; he remains on the spot where he is placed, does not cry when wet or dirty. His face expresses sadness and inconsolable unhappiness. Occasionally he alternates between apathy and irritability; spells of monotonous crying and stereotyped movements occur. In spite of the tropical heat, the kwashiorkor patient likes to cover himself with bedclothes evidently seeking warmth and darkness. Sorrow and unhappiness caused by the incomprehensible loss of mother's love is an important factor resulting in a chain-reaction which finally produces the kwashiorkor syndrome. An important consequence is the loss of desire for food . . . severe anorexia.

(3) Gastrointestinal manifestations: Anorexia is probably of psychic origin and not produced by the monotony of the starch diet. Persistent refusal to take food occasionally necessitates artificial feeding, which is often followed by vomiting. The most important intestinal trouble is diarrhea, sooner or later appearing in practically every case, loose stools varying in frequency, consistency, volume, color and containing mucus and undigested food particles, and rarely blood. If ascarides or other worms appear in the diarrheic bowel movements, the infant gets vermifuges and laxatives and his insufficient diet will be further reduced. Helminthiasis is a common condition in African adults and children, but not an etiologic factor in kwashiorkor. Diarrheas are probably not initiated by the starch food itself; inevitable infections due to the unhygienic environment, or parenteral febrile infections, start the intestinal trouble. Whatever the primary cause may be, diarrheas mark the onset of a chain reaction. Rapid passage pre-

vents absorption, causes loss of water and electrolytes and leads to chemical alterations in blood and tissues. Bacteriologic studies have not revealed evidence of a specific germ. Permanent loss of nutriment by diarrheas may lead to waste of body substance, to atrophy and marasmus.

Lesions on the tongue and mucosa in the mouth, cracks of and around the lips are signs of avitaminosis, superimposed on the protein deficiency disease. The combination of classical kwashiorkor with pellagroid or beri-beri manifestations has been named "Pluricarential", or "Multiple Deficiency Syndrome".

(4) Edema: Swelling caused by fluid accumulation in the subcutis is a most impressive feature, present in the great majority of kwashiorkor cases, but not an obligatory sign. There have been observed, on rare occasions, cases of typical kwashiorkor without edema; on the other hand, the appearance of edema is a well-known symptom in Mehlnährschaden and other malnutrition syndromes. Kwashiorkor edemas are of nutritional origin. Malnutrition and diarrheas cause hypoproteinemia in the blood; altered osmotic pressure and increased permeability result in fluid accumulation in the tissues. It is often an early sign, appearing first on the dorsum pedis, then gradually develops on legs, arms, face and in the body cavities. The intensity and extension varies with season and availability of food. The first appearance occasionally follows afebrile gastrointestinal disturbance. The malnutrition-edemas are characterized by their reversibilty. A rapid disappearance after an adequate protein diet is followed by a considerable drop in body weight, revealing an extreme loss of body substance, subcutaneous fat and muscle substance. This condition would suggest considering marasmus as a phase in the course of the kwashiorkor syndrome.

(5) Dermatoses: Skin lesions are very impressive manifestations, but not essential; if present, they are of great value for diagnosis. There have been cases of kwashiorkor without any skin alteration. European pediatricians and nutritionists point to the rashes in different types of malnutrition, similar but always milder and less characteristic. The combination of protein deficiency with a superimposed avitaminosis, especially pellagra, makes the situation still more complicated. In a fully-developed case, the appearance of the skin is very impressive. Ferro-Luzzi[14] proposed to reserve the name kwashiorkor for cases with com-

plete symptomatology plus skin lesions, and call the malnutrition syndromes without dermatoses Mehlnährschaden. It seems premature to decide about the expediency of separating the two conditions on the basis of presence or absence of dermatoses as long as our knowledge about the substances necessary for maintenance of structure and color of the skin is incomplete.

The first alteration of the skin is depigmentation (Fig. 3), a change from black to brown or bronze, probably caused by an insufficient supply of substances—amino acids—necessary for the maintenance of the negro skin color. The "kwashiorkor rash" starts with circumscribed red erythematous spots, transformed within a few hours to purplish patches which become dark by repigmentation, heightened by a peculiar waxy condition. They have been termed "enamel-paint dermatoses". Gradually they spread over the body surface; confluence produces a peculiar appearance for which Williams[15] has proposed the name "crazy pavement". A variety of secondary infections and mechanical lesions of the atrophic or edematous, vulnerable skin, hyperpigmentation alternating with wet areas produce a polymorphous picture.

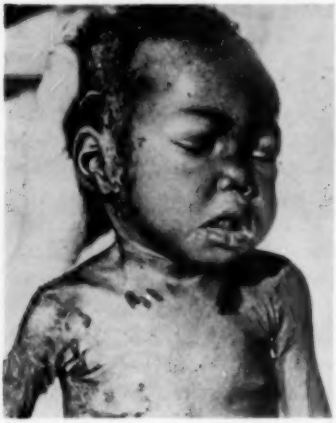

FIG. 3: Depigmentation and lesions of the skin, facial edema, alteration of the hair and expression of sadness and apathy. (From Frontali's monograph)

(6) *Hair Discoloration:* The transformation of the jet-black negro hair to red or blond is a most fascinating phenomenon. It has deeply impressed African tribes and has caused much speculation, superstition and confusion. The presence of this phenomenon is no doubt of value for diagnosis in Africa, but some authors believe that its significance is overestimated. There are cases of classical kwashiorkor without alteration of structure or color of the hair, and more important, similar dyschromasia has been observed in many malnutrition diseases, Mehlnährschaden, celiac disease (Lehndorff and Mautner)[16] "distrofia da farina" (Frontali)[4] in starved war prisoners, etc.

The hair in a pure blood negro is dark-black and curly. In kwashiorkor it changes in structure and color, it becomes thin, straight and sparse, falls out easily at the slightest pull. The change in color is described as red, blond, straw-colored, grayish, chocolate-brown. The variations could be attributed to climatic or genetic factors, racial mixture or certain food habits.

The intensity of the discoloration does not parallel the severity of the disease. Red or blond coloration restricted to the tips of the hair is called "halo effect". The phenomenon of dark hair between red tips and red roots is known as "flag sign" or "signo di bandera".

The cause of hair dyschromasia in human malnutrition can be attributed to deficient supply of special substances—amino acids—essential for the production of the normal hair color. Present knowledge of the chemistry of the hair nutrition is inadequate. I like to speculate that in Africans the color of the hair is produced by a number of pigments with black predominating. As soon as protein deficiency in the food causes an inhibition of supply of essential substances for melanin production, the black pigment is no longer restored and other pigments with other colors appear. The failure of reproduction of melanin black enables a phanerosis of other pigment colors—brown, yellow, or red. I am fully aware that this is an idea with no proof available. But confronted with an unexplained phenomenon one hypothesis is better than none, especially if a new point of view stimulates renewed research. Such speculations suggest the idea of comparing the dyschromasia of human hair with a phenomenon in the "vegetable kingdom", the autumnal color changes of the foliage from green to yellow and red, showing similar variety, but more beautiful. The appearance of yellow, red and brown during the fall is caused by the disappearance of the green pigment chlorophyl. Chlorophyl is the dominant pigment (80%); it synthesizes sugar, is permanently used up and reproduced. The changes in climatic conditions during autumn stop the renovation of chlorophyl; it disappears gradually and the other leaf-pigments, the yellow and orange *carotenes* and the reddish *antocyanines*, become visible. The basis of the dyschromasia of the foliage could be considered a result of a kind of malnutrition. But in contrast to human hair, the color-changes in the leaves are not reversible. They are a seasonal biologic event. "The botanical significance of autumnal pigment production is obscure. The beautiful tints mark an early stage

of decomposition signaling the seasonal triumph of the environment over the living plant." (J. McCormick, Natural History Magazine, N. Y., 1957[17]).

(7) Anemia: This is neither a dominant clinical sign nor of etiologic significance in kwashiorkor; until recently, only few and controversial data were available. Recent publications (McDougall and Kho Ling Kong)[18] report careful hematologic studies and extensive information can be found in Trowell's[1] new textbook. Half of the patients showed simple hypoplastic anemia; 30%, the iron-deficiency type; the megaloblastic form was present in very few patients.

DIAGNOSIS

The combination of edema, skin lesions and discolored hair in an apathetic underweight infant enables a primary diagnosis. In cases with predominant edema, kidney disease and heart failure must be ruled out. Extensive dermatoses have suggested pellagra, but in this condition, the eruptions appear in areas exposed to sun rays, the face, neck, hands and feet, while in kwashiorkor, there is never any such predilection. Pellagra skin lesions clear up promptly with vitamin treatment but do not respond to protein enriched diet. Occasionally acrodynia may be suspected by the appearance, but the "pinkies" are usually well nourished; the patients are irritable, angry or morose, but do not exhibit the sadness and unhappiness of the kwashiorkor patients. Profuse sweating may result in miliaria and extensive desquamation of the skin. Acrodynia patients complain of itching and a burning sensation in hands and feet. The burning feet syndrome was a predominant symptom in an adult negro with a definite kwashiorkor-like syndrome. (Silverblatt and Brown)[19].

UNUSUAL CASE REPORTS

These recently-published observations are of unusual interest:

(1) Akkoyunlu, et al[20] report a case of a Turkish boy born to a poor family, living near the Syrian border. Breast feeding for one year; the diet after weaning consisted of rice, gruel or soup, bread, a minimum of cheese and tea; never milk or fruits. On admission to the hospital at the age of twenty months, the infant revealed the complete picture of kwashiorkor including typical chemistry and confirmation of the diagnosis post mortem. The anamnesis reports an attack of fever and intestinal disturbances at the age of six months. Four siblings living in the same poor environment and consuming the same food, remained in perfect

health. To explain this fact, the authors suggest an "unknown constitutional" factor of etiological significance. But the term "constitutional" is just a euphemistic excuse for present ignorance. The febrile attack with diarrhea 14 months prior to the admission to the hospital could probably be considered an etiologic factor. It might have caused damage to the intestinal mucosa, impairing the activity of the cell-layer in the submucosa, which might have caused malabsorption. The case of the Turkish boy shows similarities with the "distrofia da farina" studied by Frontali and his co-workers in South Italy.

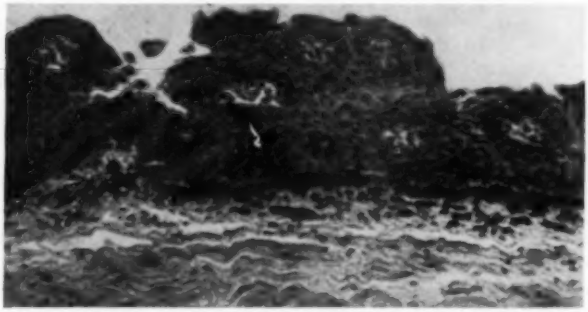

FIG. 4: Histology of esophagus revealing epithelial hyperplasia and papillomatosis. (From paper by Diamond, Vallbona, Pediatr. 27:248, 1960)

(*2*) The case reported by Diamond and Vallbona[11,12] concerns a nine-year old white boy, son of a mountain farmer in Kentucky, a "slum dweller leading a substandard existence". The family diet consisted of milk, white and corn bread, potatoes, peas and white beans, meat twice a week, mostly pork; certainly not a deficient diet. Five children consumed the same diet and only one of them became ill. The malnutrition disease did not start in early infancy, but years later. He was first admitted to the hospital at the age of nine years and returned three times until his death at the age of eleven. During this period, the picture of classical kwashiorkor became manifest. The boy's natural red hair turned to blond, gradually shed, and resulted in baldness. Post mortem examination confirmed the diagnosis: Steatosis of the liver, atrophy of the pancreas and alterations in the atrophic intestines, cystic dilatation of cells in the submucosa. Patchy hyperplasia and papillomatosis of the epithelium in the upper digestive tract was observed (Fig. 4). The authors consider these alterations—not mentioned in reports of cases in the Tropics—as an integral part of the histopathology in kwashiorkor.

In this case, as well as in the case of the Turkish boy, only one child among five acquired the fatal disease, and etiologically, I prefer a primary intestinal lesion to an unknown constitutional factor. The lesion could have been produced by severe gastrointestinal disease, for which the child was hospitalized one year prior to the onset of the disease.

Histologic findings and the manifestation of signs at a more advanced age are in favor of the concept of a lesion in the food-absorbing tissues. This may cause insufficient food absorption, the starting point for a group of reactions which finally produce the kwashiorkor syndrome.

Such ideas might lead to a transferral of kwashiorkor from the group of malnutrition diseases to malabsorption conditions.

(3) There is special interest in the publications of Hennington, Caroe, Derbes and Kennedy[21] of the occurrence of kwashiorkor in four children in one family—colored people living in great poverty in Louisiana. There were fourteen children from nineteen pregnancies. The mother was blind and deaf; the father finally abandoned the family and they had to live on charity. The family diet consisted of coffee and bread for breakfast, rice with beans and lard for lunch as well as for dinner. Sundays, beefneck or chicken with cabbage; never milk nor cheese. In this family, stress caused by the unhappy family life, could be assumed as an additional etiologic factor. But among the younger children, only two—an eleven-year-old girl and a twenty-month infant presented the complete picture of kwashiorkor; two others showed manifestations, "formes frustes".

Case histories, mostly from Africa and the tropics, report kwashiorkor in one child in a family and there is no mention of the disease in subsequent children, although neither the unhygienic environment nor the faulty feeding habits were changed. Dr. Senecal[22] (Dakar) informs me that kwashiorkor *has* been observed in subsequent infants; he also has seen the disease in twins. One can speculate that an inherited or acquired lesion in the digestive system might cause insufficient absorption and utilization of the ingested food. The so-called "formes frustes" possibly are cases which remained in the stage of infantile malnutrition. One could expect more cases of kwashiorkor among the colored and white people living in poverty in the slums of the big cities in North America, but there are none. In marasmic malnutrition atrophy has been ob-

served, but not the African type of the disease. Differences in feeding habits, shorter period of exclusive breast feeding, early additional food, always some milk or meat or fish are just enough to prevent hypoproteinosis.

(4) The most important contribution to the kwashiorkor problem is the recently-published paper by Silverblatt and Brown (1960)[19], "Kwashiorkor-like Syndrome Associated With Burning Feet Syndrome in an Adult Male".

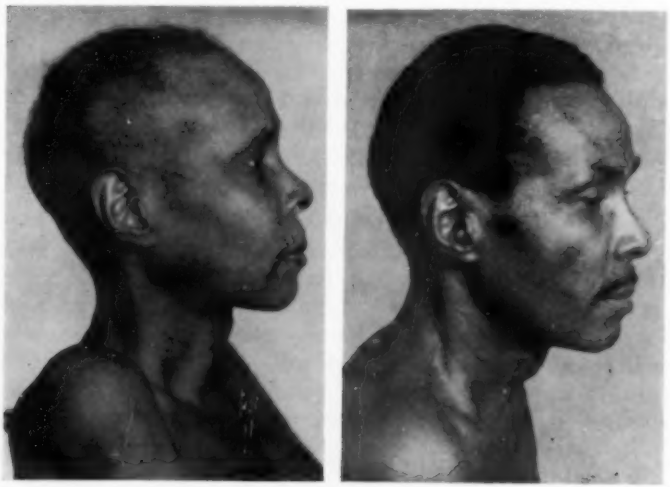

FIG. 5: 45 year-old negro with secondary kwashiorkor-like syndrome, 10 years after a subtotal gastric resection. (A) On admission: marasmus, sparce reddish-brown hair, depigmentation. (B) After treatment: weight gain, skin pigmentation and black hair. (From Silverblatt and Brown, Am. J. Med. 28:847, 1960)

A forty-five year old negro was admitted to the hospital twelve years after a subtotal gastrectomy for uclers (Fig. 5). For ten years he enjoyed perfect health, ate plenty with good appetite, then became gradually ill. Permanent diarrheas caused loss of fifty pounds; marasmus, anemia and general weakness appeared and the full symptomatology of kwashiorkor became manifest: edemas, skin rashes, hair-discoloration and shedding. The biochemical alterations in the blood serum showed pronounced protein depletion. The condition suggested idiopathic steatorrhea or sprue; gastrointestinal fistula or a dead loop were also taken into consideration, but no abnormalities could be found by surgical exami-

nation. During the preparation for surgery, the patient received an extremely large amount of protein—500 cc of plasma daily—resulting in complete recovery and disappearance of all kwashiorkor manifestations. The same clinical manifestations point to an identical pathogenesis with the infantile kwashiorkor. In African infants it is deficiency in ingestion of adequate protein. In the case of adult-kwashiorkor, sufficient food was ingested, but not digested and therefore not utilized. This case points strictly to a lesion in the digestive tract as the primary etiology. In the presented case, the damage was produced by a surgical lesion. Many observations of postoperative malabsorption have been noted: gastrointestinal fistula or blind loop (Krikler and Schrirev)[23] cholecystogastrectomy (Leitner)[24]. Identical effects were observed in inflammatory intestinal conditions (Mellikoff)[25]. According to Adlersberg, this special type could be called secondary kwashiorkor.

PROGNOSIS

Neither the intensity nor the absence of essential signs, edema, diarrhea, dermatoses, marasmus, permits a correct early prognosis. It depends on the promptness of the patient's reaction to adequate protein diet. If within a few days or a week, the infant becomes active and interested, talks and smiles, and if with increased diuresis edema disappears and appetite reappears, the prognosis can be pronounced favorable. Persistence or reappearance of edema, continuation of anorexia and apathy, indicate a serious condition.

PREVENTION AND TREATMENT

Kwashiorkor is a severe malnutrition disease afflicting infants in the tropical and subtropical zones, children of underdeveloped nations. The disease is a world problem and its prevention a world responsibility. As this disease is mainly due to poor living standards, poor personal hygiene, poor environmental conditions, prevention must first consist of improvements in these conditions. The monographs of the WHO discuss these great difficulties: agricultural problems, soil preparation for cattle-breeding, etc. The substandard of living must be elevated, but increased income sometimes results in increased alcohol consumption. Therefore, enlightenment and education are important weapons. The fight against incorrect feeding habits, food fads based on superstition, mistrust of offered food, etc., are the most important means of prophylaxis. Effective prevention should start with care for the

undernourished and overworked mother, and prenatal care established. Eighty to ninety percent of the newborns are underweight, a condition considered by the natives as an unavoidable phase in early infancy. Efforts to eliminate this fatalistic attitude are necessary. Furthermore, the mothers must be persuaded to present the babies, shortly after weaning, to a health center and accept instructions for adequate food. Local health authorities have started a promising enterprise. Young, healthy and willing native girls, trained to act as visiting nurses and dietitians are sent to the mothers to explain the cause of kwashiorkor, to instruct how to prepare and handle the offered food, and remove the mistrust against milk or new preparations of unknown aspect and taste. Native social workers are more effective than white missionaries. Such educational efforts could be supported by posters, radio lectures, pamphlets, etc. Medical textbooks should allow more space for description of kwashiorkor and malnutrition. Young physicians should be encouraged to volunteer for an assignment in the tropics and participate in the fight against starvation. This is a rewarding field for the newly-created Peace Corps.

If an infant is admitted to the hospital with a full-blown kwashiorkor syndrome, in shock, dehydrated, edematous and somnolent, the water and electrolyte deficiency and the hypoproteinemia must be corrected as quickly as possible. There is common agreement by all physicians in the tropics that the following procedures should be instituted:

(1) Intravenous transfusion of blood plasma, circa 150 cc. There is no need for whole blood transfusion.

(2) Intravenous infusion of a mixture of amino acids in saline —or better, Darrow's solution—which is similar in composition and concentration to human milk. With this procedure, excellent results have been reported, especially rapid repletion of protein deficiency in the serum. This treatment should only be used initially. Continuation without addition of sugar may cause dangerous hypoglycemia, coma, convulsions and death.

(3) Immediate vitamin supply is indicated only in cases of manifest signs of superimposed avitaminosis: pellagra, beriberi, acrodynia, etc. To improve the metabolism, various vitamins are recommended: niacin and thiamine (Frontali)[4], B_{12} (Brock and others), Vitamins A and E (Trowell et al)[1].

(4) Antibiotics: Some physicians recommend pencillin or other drugs daily for a week to prevent infections.

(5) Anthelminthics: Presence of ascaris and other worms is not an indication for immediate treatment.

(6) Anorexia: In extreme cases, feeding by tube is necessary, but the best results are achieved by loving care of a motherly nurse.

(7) Heat-Cradle to relieve the sensation of cold in hands and feet is recommended by Williams[15].

After the emergency treatment, a protein-enriched diet should be established as soon as possible. In mild cases of kwashiorkor, it may be started immediately. Dietary treatment: Successful cure has been achieved by modern food compositions, but incomplete knowledge of the chemical compositions has produced different concepts about quantity and quality of the components of food elements. Béhar[6] recommends the following: "Give a palatable food, easy to ingest and digest, rich in calories and proteins of high biologic value and low in price". There is common consent that it should be powdered skimmed milk—about 15%. This must be enriched; the most reliable method is casein hydrolysate. Additional sources of protein can be taken from locally-cultivated substances: soybeans, peanuts, cottonseed, pulverized dried fish. Vegetable proteins are considered to be of less biologic value, but they are not as expensive, are locally available, and their value can be improved by the addition of amino acids, e.g., lysine and tryptophan to wheat and corn meal. (Pharmaceutical manufacturers have prepared biscuits and presscakes.) A peanut presscake contains 50% protein and less than 5% fat. Senecal combines casein hydrolysate with glucose and amino acids. Dean[1] adds peanuts, corn or white flour and cottonseed and sugar to 15% skimmed milk powder. In attempting to improve the protein deficiency, there has been a tendency to offer an excessive amount of protein. Dean[1] warns against this as being possibly damaging or at least useless; he recommends less protein and increase of caloric value by carbohydrates and fat. Furthermore, he adds green vegetables and fruits, especially bananas. Gomez has observed a number of peculiar manifestations during recovery, and proposes the term "recovery syndrome". The main signs are enlargement of the liver, causing the pot belly; lanugo hairs appearing on bald spots; accelerated growth and gain in weight; occasionally, there is the

aspect of a moon face; blood examination reveals considerable increase of gamma globulin and in some cases, eosinophilia.

The duration of necessary confinement to the hospital varies. Milder and early cases recover rapidly; severe types need some months. Hospital treatment has reduced the mortality rate from 80% to 20%. Unfortunately, after discharge, the prescribed diet and sanitary instructions are neglected and many children are readmitted in a worse and more serious condition. The prognosis of the return cases is often unfavorable.

SUMMARY

The multiplicity of clinical, serologic and histologic manifestations suggests chain-reactions in kwashiorkor.

1. *Breast Starvation:* Primary damage results from prolonged breast feeding.
2. *Infantile Malnutrition* (pre-kwashiorkor): Caused by inadequate diet.
3. *Stress:* Psychic alterations and anorexia produce unhappiness.
4. *Intestinal Infections* (Diarrhea, etc.): Due to tropical heat and bad hygienic conditions are evidenced in earliest stage.
5. *Hypoproteinemia:* Biochemical blood alteration produced by malnutrition and malabsorption, resulting in edema, primary cause of which is changed osmotic pressure.
6. *Histopathologic Alterations:* Characteristically due to two factors—damage by protein deficiency and reaction to diarrheic stool toxins.
7. *Amino Acids:* Absence of essential substances (vitamins and enzymes) inhibits absorption.
8. *Malabsorption and Mal-utilization:* Produced by insufficient supply of building blocks for cell restitution and growth.
9. *Discoloration of Hair:* Results from absence of special amino acids necessary for melanin synthesis.

CONCLUSION

This historical background paper on Kwashiorkor underscores the importance of the disease as a world problem, and emphasizes the difficulties which may be encountered in its prevention. It is felt that such organizations as WHO, FAO, the Peace Corps and oth-

ers, should direct and intensify their efforts to educate natives in areas where knowledge of food choice, nutritional values, preparation, etc., is sorely lacking. Or where as is all too often true, damage comes from superstition and mistrust of modern scientific methods. The dedicated work of educational organizations like these, is the greatest hope for continuing the fight against Kwashiorkor . . . the pathogenesis of which remains unanswered at the present time.

REFERENCES

1. Trowell, H. C., Davis, J.N.P. and Dean, R.P.A.: Kwashiorkor, Edward Arnold, London, 1954. Trowell, H. C.: Non-infective disease in Africa, Edward Arnold, London, 1960. (Also Dean, R.P.A., Journ. Ped. 56:1960).
2. Fuhrmann, G.: Neure Arbeiten über das Kwashiorkor-Syndrom; Z. Tropenk. u. Parasit. 10:477, 1958.
3. Tamaēls, I.: Med. Klin 1959 (Review).
4. Frontali, G.: Dystrophic durch Proteinmangel bei Kinderh. (Mehlnahrschaden, Kwashiorkor, Hypoproteinose) Erg. Inn. Med. u. Kinderh. N. F. 14:199, 1959.
5. Williams, Cecily: Numerous papers since 1933.
6. Behar et al: World Review Nutr. Dis. 1:75, 1959. Ann. Acad. Sci. N. Y. 69:1957/58.
7. Czerny, A., and Keller, A.: Des Kindes Ernährung, etc., 2 Edit. Deutike Wien, 1928.
8. Gomez, et al: Paed. 20: (4 papers) 1959. Symposium Ann. Acad. Sci. N. Y. 69: 1957/58.
9. Fanconi, G. and Prader, A.: Eiweissmangeldystrophie. Helv. Paed. Acta 5:13, 1950.
10. Holt, L. E., et al: Protein and Amino Acid Requirements in Early Life, N. Y. University Press, 1960 (188 references).
11. 12. Diamond, I., and Vallbona, C.: Kwashiorkor in a North American White Male. Paed. 27:248, 1960.
13. Moodie, A. and Wellbourne, R. F.: J. Ped. 58:392, 1961. J. Prop. M. 5:94, 1959.
14. Ferro-Luzzi, G.: V. Int. Congr. Med. Trop. Istanbul 1954.
15. Williams, C. W.: Kwashiorkor: A Nutritional Disease of Childhood Associated with Maize Diet. Lancet 1. 1151, 1935.
16. Lehndorff, H. and Mautner, H.: Coeliakie. Erg. Inn. Med. u. Kinderh. 23:1927.
17. McCormick, J.: Museum of Natural History Magazine, N. Y., October 1957.
18. McDougall, L. G., and Kho Ling Kong: Ann. Paed. 194:257, 1960. Tr. Roy. Soc. Trop. Med. 54:37, 1960.
19. Silverblatt, C. W., and Brown, H. E.: Kwashiorkor-like Syndrome Associated with Burning Feet Syndrome in Adult Male. Am. J. Med. 28:847, 1960.
20. Akkoyunlu et al: Helv. Paed. Acta 12:323, 1957.
21. Hennington, B. M., Caroe, E., Derbes, V. and Kennedy, B.: Kwashiorkor: Report of 4 Cases from Louisiana, Arch. Derm. 78:157, 1958.
22. Senecal, J.: Personal letter 1961. Senecal et al: Symposium Ann. Acad. Sci. N. Y. 69:1957/58.
23. Krikler and Schrirev: Lancet 1:510, 1958.
24. Leitner, A.: Lancet II:504, 1958.
25. Mellikoff, F. S.: Amer. J. Dig. Dis. 2:738, 1957.

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Thymic Irradiation: A Historical Note

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THE present interest in the possible relationship between irradiation in childhood and the subsequent development of malignant change has led many investigators to seek out special groups of individuals who have had therapeutic irradiation in childhood. Outstanding among the groups studied are those children who received irradiation for "thymic enlargement" during the period when "status lymphaticus" and "thymic asthma" were acceptable explanations for morbidity and mortality in infancy, and childhood. Irradiation of the thymus in status lymphaticus and thymic enlargement was introduced by Doctor Alfred Friedlander† in a paper which was read before the Cincinnati Academy of Medicine on March 18, 1907 and published in the *Archives of Pediatrics* in July, 1907.[1] Friedlander's patient was treated in January and February of 1905 and thereby apparently became the first of an army of infants and children given radiation therapy to the thymic region over the next thirty to forty years.

In 1956, in the course of a follow-up study of children who had received therapeutic irradiation to the head, neck and chest, it was learned through Doctor J. Victor Greenebaum that Doctor Friedlander's original patient was living and available to provide follow-up information. Contact was established and a very gratifying reply was received. As a supplement to the current reports of extensive series of follow-up examinations, it may be interesting to compare the description by the physician concerning the circumstances of this historical occasion with that by the patient, written fifty years later and representing largely the recollections of his parents.

Doctor Friedlander began his report‡ with a historical description of medical thinking on the subject of status lymphaticus and enlarged thymus up to the turn of the century. He subscribed

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† Alfred Friedlander, 1871-1939, Pediatrician and Internist; Dean, College of Medicine, University of Cincinnati, 1935-1939.

‡ Material quoted verbatim from Archives of Ped., with permission of the publisher.

to the Paltauf theory that sudden death was extremely common in patients with status lymphaticus and added "furthermore, it is now known that patients with status lymphaticus take anesthetics very badly." He also subscribed to the concept of pressure effects of an enlarged thymus although he questioned whether the pressure was on the trachea, on the large vessels, on the heart itself, or on the mediastinal nerves. He cited the report by Heinecke (1903) on the effects of x-ray on lymphoid structures and accepted Heinecke's suggestion that shrinkage of the thymus in humans might be initiated by x-radiation with respect to the "desperate case" he then proceeded to describe.

The patient was a healthy male infant, born of normal parents after a normal pregnancy and labor. At the end of the fifth week "the mother noticed that the child had a slight cough, and also a peculiar whistling noise during inspiration." The cough quickly became worse and paroxysmal in character. During the paroxysms, there was some cyanosis, especially of the face and upper extremities. The child was examined at this time in conjunction with Doctor F. Forschheimer§ and was noted to lie on his back with the head retracted. The expression was anxious and the lips were cyanotic. Respirations were shallow and rapid and marked retractions of the diaphragmatic border were noted on inspiration. Distinct inspiratory stridor was described. A short dry cough was present and at intervals definite paroxysms, "asthmatic in charater," lasting from five to ten minutes were observed. Dullness was found over the upper portion of the sternum extending 2 and 3 cm. to the right and left of the sternum, respectively, and extending down to the level of the second rib. Deep palpation in the jugulum revealed a rounded firm mass. The spleen was palpable and there was generalized glandular enlargement. The diagnosis of status lymphaticus and enlarged thymus was made. During the next few days, the child's condition grew worse. Cough increased in frequency and the paroxysms became worse. At times, the paroxysms lasted over an hour and were accompanied by marked cyanosis and left the child exhausted. By the end of the seventh week, an area of dullness was noted in the right interscapular space and marked edema of the hands and feet supervened.

Doctor Friedlander continues: "The rather desperate character of the case had been fully explained to the parents, who expressed

§ Frederick Forschheimer, 1853-1913. Pediatrician and Internist. Professor of Pediatrics, Ohio Medical School, Cincinnati. When the Ohio Medical School united with the Miami Medical College to form the Ohio Miami Medical College of the University of Cincinnati, he became Dean and Professor of Internal Medicine.

their willingness to allow any possible therapeutic measure to be tried. It was, therefore, decided to try the effect of x-ray. On January 30th, an x-ray apparatus was installed in the house and the first treatment given by Doctor W. H. Crane.* The child was laid on his back and a sheet of lead with fenestrum was placed so that the opening left the region of the thymus exposed. The time of the first treatment was one minute. The child was then turned and the sheet of lead so arranged that the right interscapular region was exposed. The treatment to this region lasted one minute also. No changes in the child's condition in any particular were noted after the treatment. The second treatment was given on February 1st, the exposure being three minutes each anteriorly and posteriorly." Five days later, four minute exposures were given anteriorly and posteriorly and at two day intervals for three treatments each, five minute exposures were again given. After the second of the series of five minute exposures, the general condition of the child was said to be decidedly improved. The cough was less frequent and the paroxysms were shorter. Five additional treatments were given at three day intervals. "During this time the condition continued to improve. The paroxysms became fewer in number and much less severe. During two of these days there were no paroxysms. On several occasions during this period, it happened that the child was able to sleep from one feeding period to the next undisturbed. The inspiratory stridor disappeared completely."

By the end of the eighth week, the area of thymic dullness had decreased appreciably and the edema of the hands and feet had completely disappeared. Subsequently, the condition became steadily better and the development was described as apparently that of a normal child. During the second year of life, there were several episodes of tonsillitis and large tonsils were noted. In December, 1906, the tonsils were removed and a small mass of adenoid vegetations was curetted away. The report states that no anesthetic was given. In February, 1907, Doctor Friedlander felt that the child presented no demonstrable abnormality. He believed that the case was unusual "because of the remarkably successful results of the experimental use of the x-ray therapy."

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* William H. Crane, 1869-1906. Professor of Chemistry, Medical College of Ohio; Director of Municipal Laboratory, Cincinnati, Ohio. According to an article written by Alfred Friedlander in American Medical Biographies, "he was an amateur photographer of rare skill, an excellent linguist and a thorough musician." Apparently, in the early days of roentgenology, the "laboratory scientist" was a natural candidate to explore the new method of diagnosis.

The patient's report (1956) is as follows: ". . . Naturally, I have no personal memories of the incident, which took place around Christmas 1904 when I was a few weeks old. Fortunately, however, both my parents are still alive and well—one at 83, and the other at 80—and have given me a very circumstantial account of what took place. . . .

"Apparently the enlarged thymus showed up several weeks after birth. I turned blue and couldn't breathe and my father used to carry me around by my legs. I was never permitted—seemingly this lasted at least one week—to lie down. Doctor Alfred Friedlander, Doctor Fred Forschheimer and Doctor Julius Eichburg* were all in attendance. They suggested sending to Chicago for an x-ray machine—there were apparently none in Cincinnati—since they had heard that it had been successful in reducing other glands. When it came, no one knew how to use it or for how long. Finally, someone suggested cutting a hole in a tin-foil, and my father produced a silver dollar for the purpose. The rays were shot through this hole for about a minute, with the almost immediate result that the swelling was reduced and the breathing became easier. The treatments were continued for about ten days. The thymus by then was normal and has never been enlarged since. Doctor Crane, who handled the x-ray machine, later died of burns from, I gather, an x-ray machine.†

"I have never had occasion to take a general anesthetic, but have been assured by half a dozen doctors that the theory that ether was perhaps a danger to ex-thymus cases has been exploded. My health has been consistently excellent." A subsequent communication in June of 1959 states that the good health continues

COMMENT

Apart from its interest as a vignette of radiologic practice in relation to pediatrics at a time when the association of these two disciplines had just begun, the above report is of interest with respect to its being the longest follow-up of a patient treated in infancy for an "enlarged thymus." No adverse effect, and particularly, no functional or malignant change in the thyroid gland have been observed.

* Doctor Julius Eichburg, 1859-1916. Professor of Materia Medica and Therapeutics, Ohio Miami Medical College.

† Doctor W. H. Crane died suddenly in May, 1906 while addressing the Cincinnati Academy of Medicine, probably from an acute coronary infarct.

From the vantage point of fifty years later, it would appear that the first patient fore-shadowed his followers in several ways. It is now generally accepted that the signs and symptoms for which the children were given radiation therapy were not produced by thymic enlargement but by other, unrecognized conditions. A definitive diagnosis other than "status lymphaticus" was not established in Dr. Friedlander's patient.

The difference between the physician's factual report of the course after the radiation therapy and that which the patient received through his parents is informative. Unquestionably, the events were crowded together in the memories of the parents, affected as they were by the distortions of emotion and time.

The effect of lay enthusiasm on medical fads as illustrated by the history of the "almost immediate result" may well have played a role in the development of professional acceptance of thymic irradiation subsequent to the publication of Doctor Friedlander's report.

The incident of the silver dollar probably refers to the use of the coin as a template for the aperture in the "fenestrum." The fear of unusual hazard from anesthesia, expressed in the published report, was apparently firmly impressed on the parents and in turn on the patient who, to this day, has an acute awareness of anesthesia risks.

REFERENCE

1. Friedlander, A. Status lymphaticus and enlargement of the thymus: with report of a case successfully treated by the x-ray. Arch. Pediat., 1907, 24, 470-501.

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Diagnosis and Treatment of Bronchial Asthma in Children

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IT IS probably no more difficult to diagnose and treat bronchial asthma in children than it is in adults. Nevertheless, the problems are different, and—to many physicians—less familiar even though about 20 per cent of asthmatic patients acquire the disease in infancy.[1] In children, asthma is apt to be particularly severe. Dees[2] notes that of 243 deaths due to asthma in minors in 1953, 80 (33 per cent) were among children less than one year old, and another 80 among children one to five years old. For this reason, prompt diagnosis and vigorous treatment are vital.

DIAGNOSIS

Classically, bronchial asthma is defined as an allergic reaction in the bronchial tree characterized by wheezing, dyspnea, and cough productive of thick, tenacious sputum.[3,4] However, symptoms in children may differ from those in adults. In adults breathing is generally slowed; in children the respiratory rate may be increased, and wheezing may be absent or masked by respiratory infection. On the other hand, there may be pronounced wheezing without asthma. Croup, pertussis, pancreatic cystic fibrosis, hyperventilation syndrome, congenital stridor, pulmonary neoplasm, pneumonitis, or a foreign body in the trachea or bronchus are only a few of the causes of atypical, non-asthmatic wheezing.

Despite these differences, diagnosis of asthma in children is based on the same principles of painstaking patient history and clinical examination used to diagnose the disease in adults.

HISTORY

The busy practitioner usually doesn't have the time for the formal history-taking recommended in most textbooks, since this generally covers two to three pages. Instead, a short outline like the suggested Allergy History Form which follows, if intelligently filled out, will be ample for practically any case. The year preceding the visit to the physician is particularly important.

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The parents may not be able to recall the child's condition in early years, but usually are fairly certain of his health for one year past. In questioning the parents about the child's asthmatic attacks, it is helpful to establish the relation, if any, to seasons. Seasonal asthma suggests an allergy to pollens, molds, or seasonal foods; year-round asthma suggests allergy to house dust or animal danders, and ordinary foods. Chronology is most readily related to holidays or to the school year.

ALLERGY HISTORY

NAME..... AGE..... DATE.....

ADDRESS..... SCHOOL LEVEL.....

1. C.C. with age at onset: .....
2. A) Occupation of Family: .....
   B) Animal contacts: 1)canary 2) cat and 3) dog 4) rabbit 5) parakeet
   C) Bedding: 1)mattress 2) pillow 3) number of beds in the room
   D) Insecticides: 1) Larvex..... 2) Black Flag.....
   3) Flit..... 4) other.....
3. Anamnesis: .....
4. Relevant Etiology: .....
5. Past History: A) infections: .....
   B) nose and throat operations: .....
   C) other atopic forms: .....
6. Family History: .....
7. Diagnosis: .....

Premonitory Complaints: Sometimes a clue to the type of allergen responsible for the asthma attack is given by the premonitory complaints. Sneezing, or itching in the throat and over the chin or chest, may precede an attack due to an inhalant; flatulence, indigestion, or headache may precede an attack induced by food.

Foods: A relation to foods is usually rather easy to establish in infants because of their limited diet. Boiling their milk for 20 minutes in a double boiler often changes the proteins enough to establish whether milk is the allergen. In older children it is helpful to know what foods the parents think cause the allergic response. However, their opinion should not be accepted without supporting evidence. A mother's assertion that her son's lips and eyes swell when he eats fish may mean that the child is sensitive to

fish; but it may also mean that he is sensitive only to the sauce she puts on it. On further questioning it may turn out that the child does eat fish at times without showing an allergic reaction.

Occupation: A standard question when interviewing adults, occupation is often omitted when the asthmatic is a child. However, work done by all members of the child's family may have an important bearing on the case. A father who works with cattle may be the source of dander to a child sensitive to cow hair.

Drugs: In questioning the parents, inquire carefully into any medicine the child may be taking. Children often are sensitive to aspirin, and penicillin is a prominent offender. A wide number of other drugs are of course capable of causing allergic manifestations.

Diets: When faced with an allergy, as in bronchial asthma, some physicians on general principle eliminate eggs, wheat and milk from the child's diet. There is frequently no sound reason to deprive a child of these important foods. Instead, elimination diets should be followed strictly but critically, and food diaries should be kept day by day to record the foods eaten and the presence or absence of symptoms. Proper intradermal skin-testing provides a reliable and final answer in questionable situations. This procedure should not be delayed, regardless of the patient's age or physical condition, if symptoms are persistent.

Miscellaneous: As with adults, you will want to know about the family's pets and domestic animals, but neighbors' pets and animals may be equally important.

Because children usually share a bedroom, when you inquire about the child's bed and bedding, also ask about other beds or upholstered furniture where he sleeps.

Insecticides, particularly pyrethrum, are important causes of allergy in children, perhaps because children are apt to crawl on or examine closely rugs, plants or other treated objects.

SKIN TESTS

While it is an unnecessary risk to make skin tests for known allergens, systematic sensitization studies are often necessary. It is a good idea to number the allergens and to write these numbers on the child's arm with a skin marking pencil or an eyebrow pencil. The intradermal test is made just to the left of the number.

Those substances which are known to produce violent constitutional reactions such as fish, shellfish, nuts, mustard, eggs, coconut,

pollens, molds, animal danders, cottonseed, kapok seed, flaxseed, and LePage's glue, must be tested in a 1 to 1000 dilution of a 5 per cent extract. If this test is negative, a 1 to 10 dilution of a 5 per cent extract may be tried. For other substances, a single test using a 1 to 10 dilution is generally safe. Some allergists recommend that children not receive tests with potentially dangerous substances such as cotton-seed, flaxseed, or mustard. However, these may be the very substances causing the asthma, and it is valuable to test for them. If the child reacts, the allergen must be conscientiously and scrupulously avoided. But if the child is not sensitive, he and his parents need not be bound by the inconvenient, rigorous environmental control that a reaction demands. In 20 years, I have not seen a constitutional reaction when these allergens have been administered in a 1 to 1000 dilution of a 5 per cent extract. (Patients with known clinical sensitivity were, of course, not tested).

Infants up to the age of 6 months may react very strongly to allergens, but on the whole are no more highly sensitive to skin tests than older children. Some infants react to dilute solutions while others do not react except to more concentrated ones. No matter what dilution the child reacts to, the violence of the skin reaction has very little correlation with the severity of the clinical manifestations. Some children with very mild skin reactions have very severe clinical symptoms. The reverse is also true. Since only about 12 allergens can be tested at each visit, it takes a long time to complete the tests. Regrettably, there are no short cuts possible. However, it is possible to eliminate certain substances from the tests. We have found that testing with fruits and vegetables is of little value. Fruits give positive reactions in about 50 per cent of those tested and—except for beans, soy beans, peas, and corn—so do vegetables. Obviously, children are clinically sensitive to these substances very much less often than the tests indicate, and until better fruit and vegetable extracts are made, these tests might well be omitted.

TREATMENT

Proper management of the asthmatic child depends on scrupulous avoidance of all allergens, desensitization to allergens that cannot be avoided, elimination of foci of infection, resolution of emotional problems, and drug therapy. Treatment is the same as for adults and only desensitization and drug therapy need special comment.

Desensitization: Practically-speaking, desensitization is worth-

while only for inhalant allergens. Ogden and Fuchs[4] estimate that desensitization with inhalant antigens is successful in about 85 per cent of patients. We do not attempt desensitization for food sensitivity since the food may be avoided. Commercial treatment sets for inhalant allergens may be purchased and are satisfactory. Pollen antigens are standardized according to the unit of Cooke and Stull—0.00001 mg. protein nitrogen per ml. Since 1945 all the pollens we have used have been incorporated into a gelatin adjuvant[5] because they produce fewer and less severe constitutional reactions than saline extracts. With gelatin preparations, reactions can readily be controlled with only one or two antihistamine tablets in contrast to the violent and difficult-to-control reactions which occur with saline extracts.

However, even with gelatin extracts, untoward reactions are an ever-present danger, especially when the child is extremely sensitive or the antigen is especially potent. Epinephrine (Adrenalin: Parke-Davis; Epinephrine: Wyeth) 1:1000 should always be ready for use in a sterile hypodermic syringe when antigens are injected. Inject 0.4 cc. of epinephrine at the first sign of a reaction. A sterile solution of diphenhydramine (Benadryl: Parke-Davis; Hyadrine: Searle) 20 mg. given with the epinephrine in the same syringe is more effective in relieving untoward reactions. All children should remain in the office for 15 minutes after treatment and those prone to reactions should remain for 30 minutes. The child should have antihistamine tablets to take if a reaction occurs after he leaves the office; one tablet when symptoms first occur and another 15 minutes later if symptoms persist.

Injections of antigen extracts should be given subcutaneously at weekly intervals while the dosage is being increased. If by chance the interval between two injections is more than two weeks, the dose should not be increased. The dose may be repeated, however, at any interval up to four weeks. If more than four weeks elapse, decrease the dosage 25 per cent for each week over four. When maximum recommended or tolerated doses have been reached, the interval between injections can be lengthened to two weeks, then three and finally four weeks. At signs of reactions, the intervals should be shortened and the dose be repeated or reduced.

DRUG THERAPY

Drug therapy is most important during the period of skin-testing and desensitization. The most effective drugs in the treatment of

bronchial asthma are bronchodilators such as ephedrine and theophylline; expectorants, particularly potassium iodide, and sedatives. Methoxyphenamine (Orthoxine: Upjohn) is also a good bronchial dilator, and of particular value for children who have adverse reactions to the more effective ephedrine and theophylline.

For most children, however, we prefer administering a bronchodilator, expectorant and sedative in one dose. Children often resist medicine because it sets them apart from their friends; the more drugs they have to take at a time, the more they resist For this reason it is always desirable to make drug therapy as simple as possible. The most useful preparation in the treatment of asthma in my experience is Quadrinal (Knoll), an effective and convenient preparation of ephedrine and a theophylline salt in a favorable ratio, with phenobarbital and a satisfactory amount of potassium iodide (5 grains). The theophylline is supplied as the calcium salicylate salt; only slightly soluble in the stomach, it provides a desirable prolonged effect without causing gastrointestinal irritation. Phenobarbital overcomes any excessive nervous excitation. Children tolerate Quadrinal very well and definitely prefer the preparation to receiving these four drugs separately. The usefulness of Quadrinal is further indicated by the fact that parents request it for their children in preference to other drugs.

With Quadrinal, we find it helpful to administer isoproterenol (Isuprel: Winthrop; Nephenalin: Leeming) or epinephrine in a nebulizer four times daily. By these means the bronchial tree is made more patent and incrustations are constantly removed by expectoration.

Antibiotics are an important part of therapy. In our experience, the white blood count is by far the earliest and most sensitive indicator of infection and more reliable than fever, sedimentation rate, C-reactive protein, or changes in the sputum. Broad-spectrum antibiotics are most effective—oxytetracycline (Terramycin or Cosa-Terrabon: Pfizer), tetracycline (Tetracyn or Cosa-Tetrabon: Pfizer; Achromycin: Lederle; Tetrex: Bristol), erythromycin (Erythrocin: Abbott; Erythromycin: Upjohn; Ilosone: Lilly). We have not found prophylactic therapy with antibiotics to be useful although others have. Oral antibiotics in general are less likely to sensitize than subcutaneous or intramuscular ones.

Antihistamines, of course, are invaluable for nasal symptoms. When needed, they should be administered after meals. The one

with the least sporific effect appears to be phenindamine tartrate (Cerose: Ives-Cameron; Thephorin: Roche). Chlorprophenpyridamine malcate (Chlor. Trimeton: Schering; Teldrin: Smith, Kline & French) produces slightly more drowsiness than phenindamine, but less than tripelennamine hydrochloride[6] and other antihistamines. For this reason, we prefer phenindamine for daytime use and other antihistamines at night. Like adults, children of course differ in their reactions to antihistamines. Arbesman[7] at this clinic some years ago noted that for some unknown reason, various antihistamines of the same class are more effective and have fewer side-effects in one patient than in another.

Hormonal therapy with cortisone, hydrocortisone, prednisone, prednisolone, or corticotropin is of particular value in the severe intractable types of asthma. The steroid most frequently used in our clinic is cortisone 25 mg four times daily.* This dose is reduced by 25% per week as the symptoms disappear. We have continued this therapy for as long as one year without untoward effects. In fact, we have had fewer side reactions with cortisone or prednisone than we have had from sulfa drugs, penicillin, and certain of the broad-spectrum antibiotics. On careful observation of these children we have yet to find glycosuria, changes in bone structure or growth rate, or any other indication of detrimental action. However, steroids are used only after all other therapy has failed and we discontinue them as soon as practical.

SUMMARY

Diagnosis and treatment of bronchial asthma in children is not greatly different than in adults. Diagnosis depends primarily on clinical observation, with laboratory tests serving as adjuncts. Skin tests should be individualized according to the patient's history. Treatment depends on avoidance of allergens, desensitization to allergens that cannot be avoided, elimination of foci of infection, resolution of emotional problems, and drug therapy.

The drugs most valuable in bronchial asthma are bronchodilators (epinephrine, ephedrine, theophylline, etc.), expectorants (potassium iodide, ammonium chloride), sedatives, and antihistamines. The most frequently used are undoubtedly ephedrine, the xanthines, potassium iodide, and sedatives.

* Note: We changed from prednisone to cortisone because cortisone was found eleven times less growth suppressing than prednisone.

In treating children it is always of advantage to make therapy as simple as possible by using single dose preparations. For the last four years we have particularly favored a preparation of ephedrine, atheophylline salt, phenobarbital, and potassium iodide (Quadrinal: Knoll) which is especially well-tolerated, effective, and economical.

REFERENCES

1. Nilsson, D.C.P.: Nebraska M.J. 43:90, 1958.
2. Dees, S. C.: A.M.A. Dis. Child. 93:228, 1957.
3. Unger, L., et al.: J. Pediat., 52:39, 1958.
4. Ogden, H. D. and Fuchs, M.: J. La. State Med. Soc. 111:175, 1959.
5. Spain, W. C., et al.: In Cooke, R. A.: Allergy In Theory and Practice, Philadelphia, Saunders, 1947, p. 541.
6. Bancroft, C. M.: Ann. Allergy, 15:297, 1957.
7. Arbesman, C. E.: J. Allergy, 19:178, 1948.

341 *Linwood Ave., Buffalo 9*

Activities of The Poison Control Center . . .

TRIOXYMETHYLENE (DEODORANT) POISONING

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New York

THIS 22-month infant ingested a "few crumbs" of Cleer-O-Disc, a deodorant tablet described by the mother as a "block". The child complained of a bitter taste and the mother called the Poison Control Center for advice. She was advised to induce vomiting and to call a family physician since the composition was unknown at this time. A follow-up form was sent to the mother requesting that she fill it out. In addition to filling out the form carefully, the mother also forwarded a small amount of the incriminated product in a piece of wax paper. The completeness with which the mother filled out the report as to the mode of occurrence is worth reporting since many reports which we receive are regretfully lacking in detail:

> "I was washing the supper dishes and Billy was playing nearby. (I usually keep the bathroom chain locked as he likes to play with the water in the bowl) but this time it was open and he went in and came out crying and pointing to his mouth. I could see some white crumbs in it and quickly washed it out with water and made him spit it out. I went in the bathroom to find out what he ate (I also keep the garbage can in there) and noticed some white stuff on the floor. It was small pieces from the deodorant I use in the can. He must have spit most of it out when he found out it didn't taste good. I tasted it—it tasted bitter. He didn't act sick, but I thought I better call your poison center and make sure before I called my doctor for treatment, which he didn't need. I gave him his supper and milk. He has been fine so far and has more pep than I do. Thanks for your help".

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When the product was examined at the Poison Control Center the odor of paraformaldehyde was obvious even though the product was perfumed. The product was submitted to our laboratory for confirmation and a letter was sent to the reported manufacturer requesting information on its composition. We were informed that they could not give us information because the product was manufactured by another firm. However, they stated as follows:

> "We can tell you that this product is, generally speaking, non-poisonous and non-toxic. However, if the person ingesting the tablet happens to be allergic to any of its ingredients, the result may be nausea, cramps and vomiting.
>
> "We could supply you with an antidote. However, we believe it would be better if you would contact the manufacturer, as we are sure they can supply you with all the information you will need".

The manufacturer informed us that the product was trioxymethylene which is of course the less known name for paraformaldehyde. It is interesting to note that the Manufacturing Chemists Association recommends that paraformaldehyde be labeled with a skull and cross-bones and gives the usual first aid information for poisons; i.e., to give a tablespoon of salt in a glass of warm water and to repeat until the vomiting fluid is clear. They also advise giving milk and white of egg beaten with water. This is a good example of the reticence of both the manufacturer and the distributor of hazardous products—a situation which should be remedied on a national scale by the new Federal Hazardous Substances Labeling Act.

In the last 6 years the Poison Control Center has received several hundred calls on deodorant materials. Most of these materials consist of perfumed paradichlorbenzene. Interestingly enough many of these ingestions involve the deodorant block distributed by diaper laundries as part of the diaper disposal container.

These minor ingestions of paradichlorbenzene have been almost uniformly uneventful. Because of this favorable experience, the presence of paraformaldehyde as a household deodorant material was most unexpected and startling. The use of such hazardous deodorant materials should be vigorously discouraged in household products. This particular product was dispensed in the form of a 2-gram tablet which actually contributes greatly to the hazard potential since tablets are usually thought of as medicaments and associated with ingestions even by very young children.

Following is a list of ingestions reported during a recent weekend:

Substance Ingested	*Age*	*Sex*
Acetic Acid and Ammonium Chloride	27 yrs.	F
Aqua Lina (Bleach)	20 yrs.	F
Aerosporin (Polymyxin beta sulfate)—Ear medication	2 yrs.	F
Aluminum Foil	3 yrs.	F
Ammonia	2½ yrs.	F
Ammonia and Clorox (inhaled fumes)	25 yrs.	F
Anacin	Unknown	Unknown
Aspirin	Unknown	Unknown
Aspirin	2 yrs.	M
Aspirin	3 yrs.	M
Aspirin	2 yrs.	F
Aspirin, Baby	3 yrs.	M
Aspirin, Baby	1½ yrs.	F
Aspirin, Baby	2 yrs.	M
Babo Cleanser (Scouring powder)	2½ yrs.	M
Battery from Flashlight (ingested material on)	1½ yrs.	F
Bluing, Laundry	3 yrs.	M
Camphor Ball	1½ yrs.	M
Captan and Dieldrin (Fungicide; Insecticide)	7 yrs.	M
Carbona Cleaner	15 mos.	F
Carbona Cleaner	17 mos.	F
Cement	2 yrs.	M
Cement (bit on tube)	1½ yrs.	M
Cement (for aquaria)	16 mos.	M
Cerumenex (Cerapon solution)—For removal of ear wax	2 yrs.	M
Chalk	15 mos.	M
Chalk	1½ yrs.	M
Chewing Gum	29 mos.	M
Cigarette in soda water	2 yrs.	M
Clorox (Bleach)	2 yrs.	M
Clorox (Bleach)	40 yrs.	F
Clorox (Bleach)	1½ yrs.	M
Coricidin (Chlortrimeton maleate, etc.)—Antihistamine	1½ yrs.	F
Corn Remover	3 yrs.	M
Corn Remover	2 yrs.	M
Corn Remover	5 yrs.	M
Daprisal (Amphetamine sulfate)—Analgesic and stimulant	29 yrs.	F
Deodorant	Unknown	Unknown
Diaparene (Disinfectant)	1 yr.	F
Diazinon and Chlordane (Insecticides)	Unknown	M
Doriden (Sedative)	64 yrs.	F
Doriden (Sedative)	Unknown	Unknown
Face Powder (inhaled)	2½ yrs.	F
Fertilizer	3½ yrs.	M
Flashlight Battery	18 mos.	M
Fluid in Teething Ring	10 mos.	M
Fluorescein (Resorcinolphthalein)—Diagnostic aid	Unknown	Unknown
Fly Cake (Insecticide)	Unknown	Unknown
Fly Killer (Insecticide)	2½ yrs.	M
Gum	Unknown	Unknown
Hair Conditioner	Unknown	Unknown
Hair Tint	2 yrs.	F
Home Permanent Preparation	Unknown	Unknown
Ink	3 yrs.	F
Insect Stick	2 yrs.	M
Iodine	23 mos.	F
Javelle Water and Lestoil (Bleach; Detergent)	3½ yrs.	M
Lead Pencil	2 yrs.	F
LePage Liquid Solder	2 yrs.	F

Substance Ingested	*Age*	*Sex*
Lestoil (Detergent)	Unknown	F
Librium (Tranquilizer)	64 yrs.	F
Limestone	2 yrs.	M
Lipstick	3 yrs.	M
Liquid Bluing	2 yrs.	M
Lye	1½ yrs.	F
Lysol (Disinfectant)	37 yrs.	F
Lysol (Disinfectant)	9 mos.	M
Make-Up (Max Factor)	2 yrs.	F
Mascara	15 mos.	M
Matches	8 mos.	Unknown
Match Heads	1 yr.	F
Methapyrilene Hydrochloride (Antihistamine)	Unknown	Unknown
Methedrine Hydrochloride (Stimulant)	Unknown	Unknown
Moth Balls	2 yrs.	Unknown
Moth Balls	18 mos.	M
Moth Flakes	1 yr.	M
Mr. Clean (Detergent)	2 yrs.	M
Naphthalene	15 mos.	F
Neo-Synephrine Hydrochloride	11 mos.	M
Nitrates	26 yrs.	F
Nurexform (Lead arsenate)—Insecticide	Unknown	Unknown
Oil, Baby	11 mos	F
Oil Colors	1½ yrs.	M
Pain Killer	20 yrs.	F
Paint Fumes (inhaled)	Unknown	Unknown
Paregoric	2 yrs.	Unknown
Paradichlorbenzene	2 yrs.	M
Perfume	3 yrs.	M
Perfume	2 yrs.	F
Perfume	2 yrs.	M
Phenobarbital	3 yrs.	F
Poly-Vi-Sol (Vitamins)	6 yrs.	M
Powder, Baby	1 yr.	M
Preludin (Phenmetrazine hydrochloride)—Reducing agent	35 yrs.	M
Rat Poison	3 yrs.	M
Rat Poison	10 mos.	M
Refrigerant Gas	20 days	F
Roach and Ant Killer	Unknown	Unknown
Rootone (Agricultural chemical)	Unknown	Unknown
Sedacaps (Methapyrilene)—Antihistamine	16 yrs.	F
Shoe Polish	2 yrs.	F
Shoe Polish	17 mos.	M
Shoe Polish	2 yrs.	M
Soap Bubbles	18 mos.	M
Stamp Pad (Carter's Red Ink)	2 yrs.	M
Stay Wake (Caffeine and dexedrine)—Stimulant	Unknown	Unknown
Stelazine (Anticonvulsant)	15 yrs.	M
Tintex (Fabric dye)	4½ yrs.	M
Trancoprin (Chlormazanone); Phenergan with Codeine; Beer	51 yrs.	M
Tums (Antacid)	2 yrs.	F
Tums (Antacid)	2 yrs.	F
Vinegar and Bleach Fumes	Unknown	F
Washing Fluid	20 yrs.	M
White Shoe (sucked on)	16 mos.	F
Zirconium Oxide	1 yr.	Unknown
Unknown	4 yrs.	M
Unknown	43 yrs.	F

125 *Worth Street, New York* 13

(This is the tenth of a series of papers by Dr. Jacobziner)

HEMATOLOGY AND BLOOD GROUPS, edited by D.A.G. Galton and K. L. A. Goldsmith. University of Chicago Press. 176 Pages. $4.00.

For the present-day hematologist, to say nothing of the practicing generalist, the vast avalanche of investigation that has been published in the field of Hematology in the past 20 years is such that one can scarcely hope to keep abreast of all facets of this field other than that which might concern a narrow field of personal research or clinical interest. This timely volume of some 30 individual articles by different authors attempts to summarize the present available knowledge in two major areas of hematological research. It appeared originally as two issues of the British Medical Bulletin in 1959, and, the University of Chicago Press must be congratulated for making the set available generally in this country in book form. It carries the stamp of authority by reason of the unquestioned expert status of most of the authors. Many of these, such as Ingram (Hemoglobin Structure), Dacie and Mollison (Hemolytic Anemias), Race and Sanger (Blood Group Inheritance), Coombs (Anti-globulin Reaction) are the pioneers in their fields.

The style is basically historical, concise and abundantly referenced. The approach is uniformly investigative and thereby restricts its audience to serious students of hematology, although the rewards are great for the practitioner willing to spend the effort in reading and digesting the short (3-11 pages) but detailed articles.

The symposium on Hematology deals mainly with the life cycle of the red blood cells and touches on iron, folic acid and B12 metabolism, hemoglobin synthesis and structure, and normal and abnormal red cell destruction. It is significant of its scope, that only three articles mention treatment at all, two of which discuss hemolytic disease of the newborn.

The symposium on Blood Groups is complex to say the least, and suitable primarily for those with enough background in blood banking to qualify them as experts in this field. For one interested in genetics and anthropology, these subjects are thoroughly and quite learnedly discussed.

This is not a "practical" book, nor is it leisure reading. For the practicing pediatrician it is an authoritative post-graduate basic science course. It is highly recommended.

WILLIAM E. BARRY, M.D.

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*Conservative estimate based on the clinical use of FURADANTIN tablets and Oral Suspension since 1953.

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1. Kane, S.: Am. Pract. & Digest Treat. *8*:65 (Jan.) 1957.

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